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### Recovery from depression

Kaptein, Kirsten Ilja

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# *Chapter 5*



## Course of Depressive Symptoms After Myocardial Infarction and Cardiac Prognosis: A Latent Class Analysis

Kirsten I. Kaptein, Peter de Jonge, Rob H. S. van den Brink, and Jakob Korf

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### Abstract

**Objective:** The presence of depressive symptoms after myocardial infarction (MI) is a risk factor for new cardiovascular events. The importance of the course of post-MI depressive symptoms for cardiac prognosis is not clear. We therefore set out to investigate whether different courses of post-MI depressive symptoms can be identified and determine their associations with cardiac events.

**Methods:** Data were derived from the Depression after Myocardial Infarction (DepreMI) study, a naturalistic follow-up study of patients admitted for an MI in four hospitals in the Netherlands ( $N = 475$ ). Scores on the Beck Depression Inventory (BDI) during hospitalization and at 3, 6, and 12 months post-MI were analyzed. Using latent class analysis (LCA), we identified classes characterized by distinctive courses of depressive symptoms and then examined their link to cardiac prognosis.

**Results:** The prevalence of significant depressive symptoms ranged from 22.7% to 25.5% throughout the post-MI year. Five distinct courses were found: no depressive symptoms (56.4%), mild depressive symptoms (25.7%), moderate and increasing depressive symptoms (9.3%), significant but decreasing depressive symptoms (4.6%), and significant and increasing depressive symptoms (4.0%). Subjects in this last class had, statistically, a significantly higher risk for a new cardiovascular event compared with subjects without depressive symptoms (hazard ratio (HR) = 2.73;  $p = .01$ ). Controlling for baseline cardiac status and sociodemographic data did not alter the association (HR = 2.46;  $p = .03$ ).

**Conclusions:** Post-MI depressed subjects with significant and increasing depressive symptoms are at particular risk of new cardiac events. This subgroup may be most suited for evaluation of the effects of antidepressant treatment on cardiac prognosis.

### **Abbreviations**

*BDI* = Beck Depression Inventory  
*BIC* = Bayesian Information Criteria  
*CABG* = coronary artery bypass graft  
*CIDI* = Composite International Diagnostic Interview  
*DepreMI* = Depression after Myocardial Infarction  
*HR* = hazard ratio  
*ICD-10* = International Classification of Diseases, Version 10  
*LCA* = latent class analysis  
*LVEF* = left ventricular ejection fraction  
*MI* = myocardial infarction  
*PTCA* = percutaneous transluminal coronary angioplasty.

## Introduction

Approximately 25% of myocardial infarction (MI) patients develop depressive symptoms in the year after MI.<sup>1-5</sup> Several studies have found post-MI depression to be a risk factor for reinfarction and death.<sup>5-9</sup> It remains unclear whether the course of depressive symptoms is important to cardiovascular prognosis. Such information could help in the interpretation of the nature of the effect of depression on cardiac prognosis and might also guide treatment efforts for post-MI depression. In the ENRICHD study,<sup>10</sup> for example, only limited effects of active treatment of post-MI depression on depressive symptoms and no effects on cardiovascular prognosis compared with usual care were found. In part, this seems to be due to a spontaneous recovery of a considerable proportion of post-MI depressed patients in the usual care group. A detailed analysis of the course of post-MI depressive symptoms might reveal subgroups with varying courses of depressive symptoms and different risks for new cardiac events. Although in general psychiatry the importance of the course of depression has been acknowledged<sup>11-13</sup>, less attention has been paid to the course of depressive symptoms after MI. Only a few studies have investigated the development of post-MI depressive symptoms after discharge; in these studies, it was found that on average depressive symptoms persisted or decreased somewhat over the following months post-MI.<sup>4,14,15</sup> To our knowledge, however, no attempts have been made to form empirically derived classes of subjects based on their post-MI course of depressive symptoms. In this study, we will therefore apply latent class analysis (LCA)<sup>16-18</sup> for this purpose. LCA has been used to describe depressive symptoms, major depression, and psychotic and melancholic depressions<sup>19-22</sup> in cross-sectional studies. However, with LCA, longitudinal data can also be analyzed.<sup>23-25</sup> In the present study, we set out to classify MI patients according to their course of depressive symptoms and evaluate their cardiac prognosis.

## Methods

The methods of the Depression after Myocardial Infarction (DepreMI) study have been described in detail elsewhere<sup>26,27</sup> and are briefly described below.

### *Design and Patients*

The DepreMI study is a naturalistic follow-up study of the impact of depressive symptoms on cardiac prognosis in MI patients in four hospitals in the North of The Netherlands. Patients admitted for an MI during September 1997 to September 2000 were included and followed until April 2002. Patients received usual aftercare for their MI and depressive symptoms. Inclusion criteria were a) chest pain for at least 20 minutes, b) creatinine phosphokinase levels 100% above normal or creatinine phosphokinase MB levels above 10%, and c) presence of new pathological

Q waves on the electrocardiogram in at least two leads. Exclusion criteria were life expectancy of less than a year (because of noncardiac condition), too poor physical condition according to hospital staff, cognitive dysfunction, inability to speak or read Dutch, occurrence of an MI in patients admitted for another reason, and follow-up visits scheduled in a nonparticipating hospital. All participating patients signed an informed consent form. The study protocol was approved by the ethics committee review board at the participating hospitals.

### Assessments

The Beck Depression Inventory (BDI)<sup>28</sup> was scored during hospital stay and at 3, 6, and 12 months post-MI. The BDI is a widely used 21-item self-report measure to assess the presence and severity of depressive symptoms. Each symptom is rated from 0 to 3, representing increasing levels of severity, with 0 representing absence of the symptom. A score of 10 or more is generally accepted as having significant depressive symptoms, and a score of 20 or more is regarded as having depressive symptoms of at least moderate intensity. At approximately 3 and 12 months post-MI, patients underwent the Composite International Diagnostic Interview (CIDI) to assess the presence of a depressive disorder according to *International Classification of Diseases, Version 10* (ICD-10) diagnostic criteria. Sociodemographic data (gender, age at MI, living alone or not, smoker or nonsmoker, and body mass index) and information on history of depression (occurrence either more than 1 year before the MI or less than 1 year before MI) were collected during hospitalization. At approximately 3 months post-MI, neuroticism and extraversion were measured with the Eysenck Personality Questionnaire.<sup>29</sup> Vital exhaustion was also measured at approximately 3 months post-MI, using the Maastricht Questionnaire (MQ).<sup>30</sup> Severity of the index MI was represented by the left ventricular ejection fraction (LVEF), maximum cpk-mb level, revascularization, arrhythmia, and presence of heart failure. LVEF was assessed during hospitalization by echocardiography, magnetic resonance imaging, angiography, or nuclear radiography. For reasons of comparability, LVEF was dichotomized as >40% or <40%. Revascularization, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) and the occurrence of an arrhythmic event were all recorded during hospitalization. Killip class (dichotomized as 0–1 versus ≥ 2) was used to assess the presence of heart failure during hospitalization. Study end points included cardiovascular mortality and cardiac-related readmissions after discharge from the hospital. Information on potential end points was collected from hospital records and the patient's primary care physician. Two cardiologists independently evaluated the nature (cardiovascular or not) and onset of the end points. Decisions were required to be unanimous. Follow-up time was defined as the time from index MI until a) the occurrence of cardiovascular complication, b) death of the patient for noncardiovascular reasons, c) refusal of the patient to participate any further, and d) end of follow-up time. Mean follow-up duration was 2.5 years.

### Statistical Analyses

#### *Missing Values*

When one of the four BDI assessments was missing, we used the single multiple-imputation method<sup>31-33</sup> to replace the missing BDI. Single imputation can be used to replace missing data when less than 10% of the data are missing, without biasing the results.<sup>34</sup>

#### *Latent Class Analysis*

We applied LCA<sup>16-18</sup> to the 4 BDI assessments of the entire cohort. LCA is a statistical model-fitting method to identify different classes of subjects within a given data set. LCA assumes unobserved latent variables to explain the associations among observed scores and can be seen as a categorical equivalent of factor analysis, which assumes continuously distributed latent variables. Instead of giving a particular true solution, LCA produces several solutions with relative fit indices. LCA computes two sets of parameters. The first set is the latent class probabilities or class prevalences. The other set of parameters is called the conditional probabilities and estimates the probability of the observed variables, given that the individual is a member of that class. The conditional probabilities are analogous to the factor loadings in factor analysis. The Bayesian information criteria ( $BIC = \log(L) - 0.05 \times \log(n) \times k$ , where  $k$  is the number of parameters)<sup>35</sup> are generally used for the goodness of fit to determine the optimal number of groups. The smallest BIC value gives the best fit, but a difference of less than 6 will favor the higher BIC value. The null model is a model for one single class, i.e., the whole cohort belonging to the same latent class. This model is rejected when models with two or more parameters result in better fit indices. LCA requires no intercorrelations between the assessments within classes, because it is assumed that all correlations between the assessments can be explained by the latent classes. We therefore assessed the correlations between the four BDI assessments of the entire cohort and within each of the latent classes.

#### *Comparison Between Classes*

The resulting latent classes were compared on the following variables: sociodemographic data (gender, age at MI, living alone or not, smoker or nonsmoker, and body mass index), history of depression (depression more than 1 year before MI and depression less than 1 year before MI), baseline cardiologic data (history of MI, LVEF <40%, Killip class  $\geq 2$ , max cpk-mb, arrhythmic event during admission, PTCA and CABG during admission), psychometric data (neuroticism, extraversion, and vital exhaustion), and post-MI depression characteristics based on BDI and CIDI. For these analyses, we used the Pearson chi square (categorical variables) and ANOVA (continuous variables). Statistical significance was evaluated using two-sided,  $p < .05$  levels.

### *Survival Curves*

For each latent class, we calculated a Kaplan-Meier survival curve<sup>36</sup> to compare the rate of cardiac events (fatal or nonfatal) among the classes. Differences between the curves were tested with the log rank test. After that, every single class was compared against the class of nondepressed subjects by Cox regression analysis. We tested confounding due to the severity of the MI, gender, living alone, and history of MI by adding these variables in the Cox models. We included these potential confounders because of their relation with cardiovascular prognosis and with depression. We did not use the risk factors smoking and body mass index (BMI), due to a considerable number of missing values (44 and 86 cases).

### **Results**

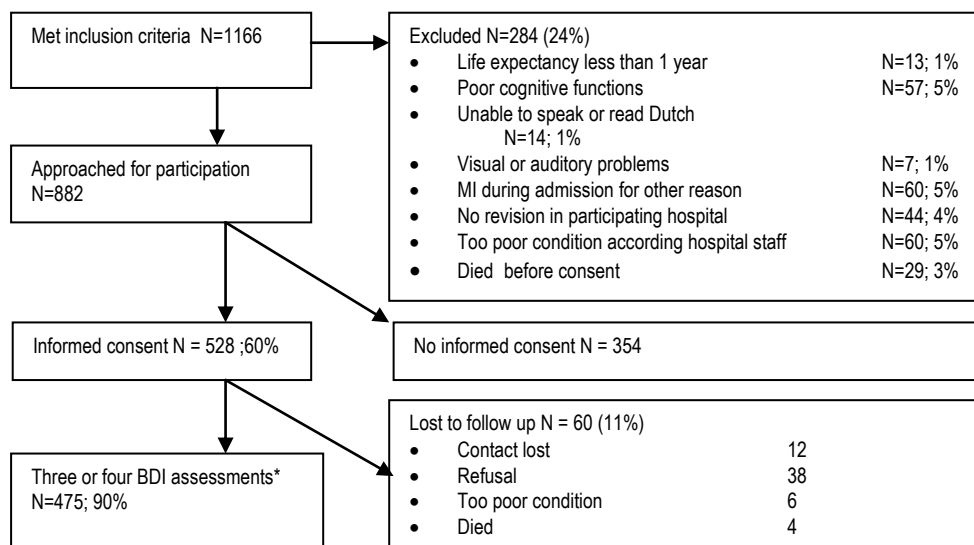
Inclusion criteria for the DepreMI study were met by 1166 patients, but 284 (24%) were then ineligible based on the exclusion criteria. Of the remaining 882 patients, 528 (60%) gave informed consent. Four hundred thirty-eight patients completed all BDI assessments, and 37 patients missed one BDI assessment, which is acceptable for conducting single imputation.<sup>33</sup> Figure 1 shows the flow chart. The 475 patients in our analyses consisted of 90 women and 385 men, with a mean age of 60.6 years. Based on the criterion of BDI  $\geq 10$ , the prevalence of significant depressive symptoms throughout the post-MI year was 22.7% during hospitalization, 23.8% 3 months post-MI, 25.5% 6 months post-MI, and 24.8% 12 months post-MI. Based on the criterion of BDI  $\geq 20$ , the percentages were 2.9%, 4.8%, 4.9%, and 5.5%, respectively. Based on the CIDI interviews administered at 3 and 12 months post-MI, 116 of 461 patients (25.2%) met the ICD-10 criteria for depressive disorder during the post-MI year. One hundred twelve (23.6%) patients experienced a cardiovascular event during follow-up, of which 21 (4.4%) were fatal.

### *Latent Classes*

For the 1-, 2-, 3-, 4-, and 5-class solutions, the BIC values were decreasing for every additional class while still resulting in classes with sufficient numbers of subjects ( $N > 20$ ). The 6-class solution gave an even smaller BIC value but contained two small classes of 6 and 7 subjects, respectively. The BIC value for the 7-class solution could not be calculated, due to a class of 0 subjects. The 8-class solution gave a larger BIC value and was therefore rejected. We chose the 5-class solution as best because it had the smallest BIC value compared with solutions with 1 to 4 classes while still having classes with sufficient subjects for further analyses (smallest class:  $N = 19$ ). Table 1 shows the BIC values of the LCA classes. The classes were characterized as 1) no depressive symptoms ( $N = 268$ , 56.4%), 2) mild depressive symptoms ( $N = 122$ , 25.7%), 3) moderate, increasing depressive symptoms ( $N = 44$ , 9.3%), 4) significant but decreasing depressive symptoms ( $N = 22$ , 4.6%), and 5) significant and



increasing depressive symptoms ( $N = 19$ , 4.0%). The course of depressive symptoms of the five latent classes is shown in figure 2. Testing the correlations among BDI scores for the total cohort and for the 5-class solution resulted in significant correlations among the BDI scores for the total cohort (varying from 0.6 to 0.8) but not within the classes (varying from -0.2 to 0.4), indicating that this model fits the data well.



**Figure 1.** Flowchart. DepreMI study. \*Beck Depression Inventory (BDI) assessments during hospitalization and at 3, 6, and 12 months post-MI.

Class Solution	BIC Value
1-Class	12,301.466
2-Class	11,361.657
3-Class	11,076.309
4-Class	10,960.316
5-Class	10,942.969
6-Class	10,889.612
7-Class	*
8-Class	10,904.243

\*Could not be calculated due to a 0-subject class.

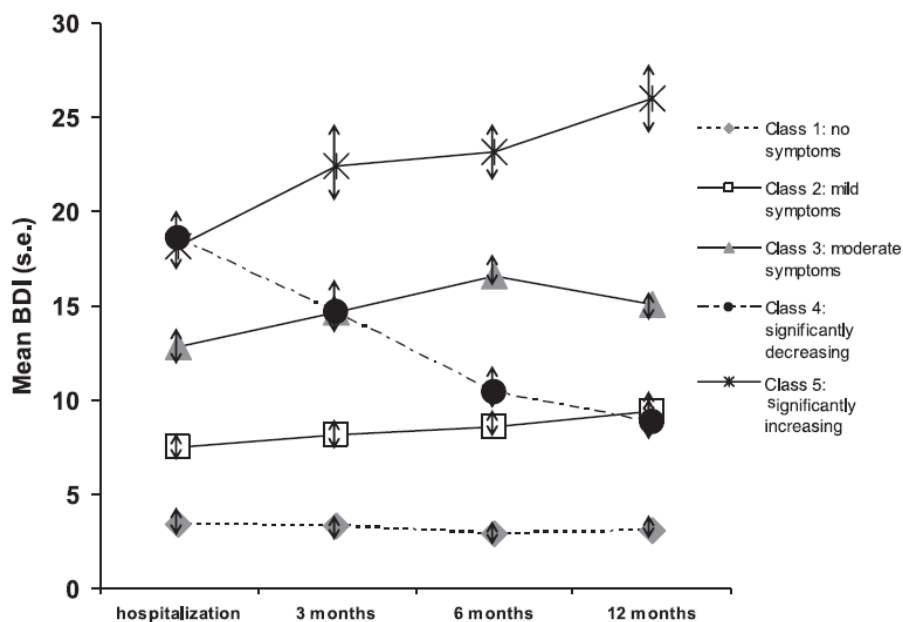
**Table 1 :** Bayesian Information Criteria (BIC) Values for the Latent Class Analysis Classes

### Comparison Between Classes

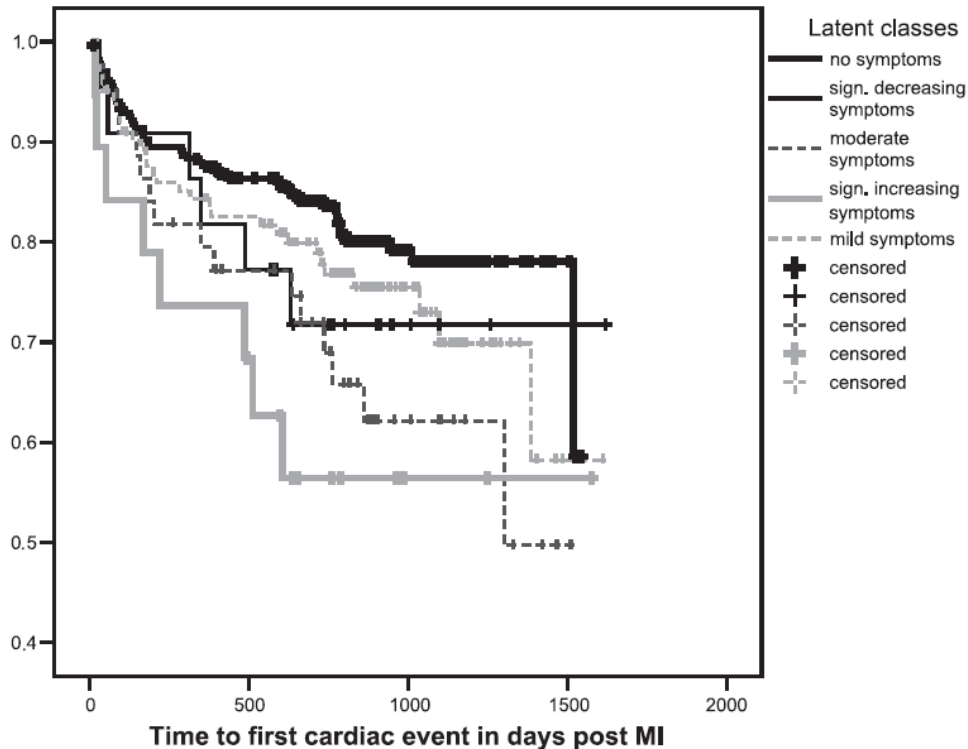
As shown in table 2, a comparison of classes on several characteristics revealed that a majority of subjects in classes 3 (moderate, increasing), 4 (significant, decreasing), and 5 (significant, increasing) developed a depressive disorder during the post-MI year. In addition, class 5 (significant, increasing) is characterized by severe depressive symptoms at all follow-up assessments. Class 4 (significant, decreasing) resembles class 5 in depressive symptomatology during hospitalization, but the presence of at least moderate symptoms of depression (indicated by BDI  $\geq 20$ ) disappears after 3 months post-MI.

### Survival Curves

The Kaplan-Meier survival curves to describe the time until a cardiovascular event for the five latent classes resulted in a significant overall difference in survival among the classes (log rank: 10.79,  $df = 4$ ,  $p = .029$ ) (figure 3). When comparing classes 2 to 5 against class 1 (no depressive symptoms), all classes tended toward higher rates of new cardiac events (hazard ratio (HR) class 2: 1.89, class 3: 1.86, class 4: 1.43, class 5: 2.73). However, only the class 5 of subjects with significant and increasing depressive symptoms had a significantly higher rate (HR: 2.73,  $p = .01$ ) (table 3). Controlling for baseline MI severity and additional risk factors did not alter the association.



**Figure 2.** Mean BDI scores of the five latent classes during the post-MI year.



**Figure 3:** Event-free survival for the five latent classes based on course of post-MI depressive symptoms.

## Discussion

The prevalence of depressive symptoms in our sample of MI patients was common: 22.7% developed significant depressive symptoms during hospitalization, which is in line with previous reports.<sup>2,3,5,7,8</sup> In contrast to most of the existing literature, we were also able to study the course of depression throughout the post-MI in more detail. We found that the presence of significant depressive symptoms was relatively stable, ranging from 23.8% at 3 months to 24.8% at 12 months post-MI. About a quarter of the subjects (25.2%) developed a depressive disorder fulfilling ICD-10 criteria during the post-MI year. By analyzing the course of depressive symptoms in more detail, we were able to identify five distinct classes: Class 1 included 56.4% of the subjects without depressive symptoms; class 2, 25.7% of the subjects who developed mild depressive symptoms; class 3, 9.3% with moderate but increasing depressive symptoms; class 4, 4.6% with significant but decreasing depressive symptoms; and class 5, 4.0% of the subjects with significant and increasing depressive symptoms.

Characteristic	Class 1 No depressive symptoms	Class 2 Mild depressive symptoms	Class 3 Moderate depressive symptoms	Class 4 Severe decreasing depressive symptoms	Class 5 Severe increasing depressive symptoms	Total	P
N(%)	268(56)	122(26)	44(9)	22(5)	19(4)	475(100)	
Socio-demographic:							
Male sex	88.4	73.0	61.4	77.3	78.9	81.1	<0.001
Age at MI time*	59.7(11.2)	62.3(11.1)	62.0(12.3)	61.5(13.4)	58.2(11.6)	60.6(11.4)	0.215
Living alone	9.7	20.5	27.3	22.7	15.8	14.9	0.005
Smoking	48.2	58.6	55.0	45.0	86.7	52.7	0.026
BMI*	27.1(4.0)	26.8(4.1)	25.7(4.4)	25.3(3.4)	25.3(3.1)	26.7(4.0)	0.088
History of depression:							
> 1 year	6.2	17.9	32.6	18.2	36.8	13.4	<0.001
< 1 year	4.2	14.5	18.6	22.7	36.8	10.4	<0.001
Post-MI Depression ICD-10 (%)	7.3	36.8	69.8	54.5	63.2	25.2	<0.001

Psychometric:							
Neuroticism*	1.9(2.3)	4.1(3.0)	7.1(2.8)	6.3(3.4)	8.4(2.9)	3.4(3.3)	<0.001
Extraversion*	5.3(2.8)	6.2(2.8)	6.5(2.3)	5.8(2.9)	5.8(2.8)	5.7(2.8)	0.018
Vital exhaustion*	6.5(5.5)	16.8(7.3)	25.5(7.8)	27.6(7.7)	30.0(5.7)	12.8(10.2)	<0.001
Baseline cardiological:							
Previous MI	12.7	13.9	22.7	13.6	21.1	14.3	0.428
LVEF <40%	22.8	21.3	36.4	22.7	21.1	23.6	0.344
Kilip class >=2	11.3	10.7	27.3	13.6	36.8	13.7	0.032
Max cpk-mb*	124.2(115.8)	106.6(128.9)	128.6(172.0)	79.9(80.3)	61.3(53.2)	115.5(123.0)	0.091
Arrhythmic event	8.6	7.4	11.4	18.2	15.8	9.3	0.414
PTCA	24.6	29.6	25.6	26.3	11.8	25.5	0.597
CABG	4.7	1.9	2.6	0	0	3.3	0.504
Cardiac prognosis							
Events (%)	51(19)	31(25)	16(36)	6(27)	8(42)	112(24)	0.026

**Table 2:** characteristics of the 5 latent classes in percentages. \* ANOVA for comparison of means (s.d.). Rest: Pearson Chi Square test. BMI = body mass index (weight in kg/length in m<sup>2</sup>).

	HR	95%CI	P
<b>Unadjusted</b>			
Class 2: mild depressive symptoms	1.43	0.87–2.37	0.163
Class 3: moderate depressive symptoms	1.86	0.99–3.51	0.055
Class 4: significant and decreasing symptoms	1.89	0.79–4.55	0.154
Class 5: significant and increasing symptoms	2.73	1.27–5.87	0.010
<b>Adjusted</b>			
Class 2: mild depressive symptoms	1.42	0.84–2.40	0.190
Class 3: moderate depressive symptoms	1.58	0.81–3.10	0.180
Class 4: sign. decreasing symptoms	1.88	0.77–4.62	0.167
Class 5: sign. increasing symptoms	2.46	1.11–5.45	0.027
Killip class $\geq 2$	1.44	0.88–2.36	1.48
LVEF $>40\%$	1.16	0.74–1.82	0.519
Max cpk-mb	1.00	1.00–1.00	0.187
Gender	1.06	0.64–1.77	0.824
Living alone	0.97	0.56–1.68	0.905
History of MI	2.02	1.20–3.25	0.04

HR = hazard ratio

**Table 3:** Cox regression analysis of Latent Classes 2 to 5 risk of new cardiac events compared to class 1 (no depressive symptoms)

Of the subjects in class 5, a majority developed a post-MI depressive disorder during the post-MI year (63.2%), which was rather similar for classes 3 (69.2%) and 4 (54.4%). Remarkable about subjects in class 5, however, was the persistence of symptoms which were of at least moderate intensity ( $\text{BDI} \geq 20$ ) during all follow-up assessments. Subjects in this class also had the highest rate of new cardiovascular events compared with subjects with no depressive symptoms ( $\text{HR} = 2.73$ ). This difference was not explained by the severity of the MI or additional risk factors ( $\text{HR}_{\text{adjusted}} = 2.46$ ). Some disagreement still exists about whether the presence of post-MI depressive symptoms is a causal risk factor for cardiac prognosis<sup>4,37,38</sup>, although in a recent meta-analysis<sup>9</sup>, consistent associations were reported. Our current findings underscore the need to look more closely to identify subtypes of post-MI depression based on the course of symptoms. Not

much is known yet about differential courses of post-MI depression. On average, depressive symptoms seem to be stable during the post-MI year, which is reported elsewhere<sup>e.g.4,11,39</sup> and is replicated in our present study. However, when looking at the specific courses of depressive symptoms, a significantly increased rate for new cardiac events was found only for one class of subjects with significant depressive symptoms that increased during the post-MI year. In contrast, another class of subjects with significant depressive symptoms during hospitalization whose symptoms decreased during the post-MI year did not have an elevated risk. A third class also seems to be of interest: subjects with elevated BDI scores during hospitalization that slowly seem to increase during the post-MI year. In this class of subjects, a majority (69.8%) experienced a depressive disorder fulfilling diagnostic criteria. Moreover, an increased rate of new cardiac events ( $HR = 1.86$ ) was found, with a borderline significance. Many of these patients will be missed when depression is only screened for during hospitalization. The following limitations and strengths of our study need to be mentioned. Our choice for the 5-class solution, although the 6-class solution had a lower and therefore better BIC value, is debatable. The 5-class solution, however, gave sufficient subjects in each of the classes instead of two small subgroups of 7 and 6 subjects found in the 6-class solution. A strength of our study is the use of a large number of subjects (475) who experienced an MI. Another strength is the use of repeated BDI and CIDI assessments and the LCA method to identify different courses of depressive symptoms after MI, which has not been applied previously in this context. Among the study limitations, the considerable proportion of excluded patients during the inclusion phases of the study should be considered. Specifically, the number of patients who did not give informed consent may have resulted in an underrepresentation of patients with post-MI depression. In order to see if our study was still representative of the population, we therefore compared our data with results reported in previous studies. Generally, an estimated prevalence of 15% to 25% of post-MI depression is reported, so our finding of 25.2% seems in line. We therefore do not expect that major bias has been introduced. Finally, as this is a new approach to describe courses of post-MI depressive symptoms, our results need to be confirmed by others using this methodology. Insight in the course of depressive symptoms after MI may be important for clinical practice. Our findings suggest that MI patients need to be followed up for depressive symptoms also after hospitalization for their index MI because in some patients, depressive symptoms may increase only then. It remains unclear whether this represents a deteriorating medical status or a negative development of depressive symptoms that stands by itself. On the other hand, some of the subjects who experience depressive symptoms during hospitalization may experience decreases in their symptoms without intervention. Such a course of symptoms might be seen as a direct reaction to the MI or even attributed to the MI due to symptom overlap (e.g., fatigue).<sup>40,41</sup> In conclusion, in our study, subjects with significant depressive symptoms during hospitalization that increased during the post-MI year had a significantly higher rate of new cardiovascular events, which was not

explained by any initial measure of cardiac impairment. The other classes, although having some differences in characteristics, showed no significantly impaired outcomes. Special attention should therefore be given to those patients with increasing depressive symptoms during the post-MI year. Although in our sample this was a relatively small subgroup, treatment of depression in these cases may lead to both improvement in depression status and to a reduction of new cardiovascular events.

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